Atropisomeric Chiral Diiododienes (*Z*,*Z*)-2,3-Di(1-iodoalkylidene)tetralins: Synthesis, Enantiomeric Resolution, and Application in Asymmetric Catalysis

Masamichi Ogasawara,[*,†,‡] Hirotaka Sasa,[§] Hao Hu,[†,‡] Yuta Amano,[§] Hikaru Nakajima,[‡] Naoko Takenaga,[∥] Kiyohiko Nakajima,[⊥] Yasuyuki Kita,[¶] Tamotsu Takahashi,[‡] and Toshifumi Dohi[*,§]

[†]Department of Natural Science, Graduate School of Science and Technology, Tokushima University, Tokushima 770-8506, Japan

[‡]Institute for Catalysis and Graduate School of Life Science, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan

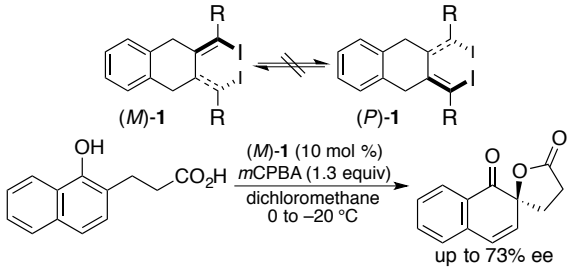
[§]College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga, 525-8577, Japan

[∥]Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya, 468-8503, Japan

[⊥]Department of Chemistry, Aichi University of Education, Igaya, Kariya, Aichi, 448-8542, Japan

[¶]Research Organization of Science and Technology, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga, 525-8577, Japan

Supporting Information Placeholder



ABSTRACT: The C_2-symmetric tetralin-fused 1,4-diiodo-1,3-butadiene derivatives, (*Z*,*Z*)-2,3-di(1-iodoalkylidene)tetralin **1a-c**, are atropisomeric and can be resolved into the two persistent axially chiral enantiomers by HPLC on a chiral stationary phase. The enantiomerically pure compounds can serve as chiral organocatalysts for dearomatizing spirolactonization to show good performances in up to 73 % ee.

"Atropisomerism" is the phenomenon of chirality by virtue of restricted rotation about a single bond.[1] The first experimental observation of atropisomerism was reported by Christie and Kenner in 1922 in a 2,2',6,6'-tetra-substituted biphenyl.[2] Since then, various atropisomeric biaryl compounds have been prepared and their single-enantiomeric counterparts have been utilized in a wide range of asymmetric reactions as useful chiral scaffolds.[3] Atropisomeric systems other than biarys, which are often referred to as "non-biaryl atropisomers",[4] include aryl amides,[5] diaryl ethers,[6] etc.,[7] and these have been rapidly developing in the last few decades.

Possibilities of alkenyl-alkenyl atropisomerism in 1,3-dienes were pointed out in the 1950s,[8,9] however, such enantiomerically resolvable dienes are rare.[10] The energy barrier to rotation about the C2-C3 bond in a 1,3-diene is generally low, and thus majority of atropisomeric dienes reported so far show slow C2-C3 bond rotation and racemize at and above ambient temperature.[8,10,11] For example, optically active dicarboxylic acid **A** racemizes completely within 22 min at room temperature.[9] The incorporation of a fused cyclic structure at the C2-C3 bond of a 1,3-diene increases the conformational rigidity of the molecule, and bulky substituents on the "inner" sides of the dienic 1- and 4-positions force the diene to adopt a nonplanar chiral conformation. While these structural modifications increase the racemization barriers in atropisomeric 1,3-dienes, cyclopentane-fused (*Z*,*Z*)-1-silyl-4-stannyl-1,3-diene **B**[12] and cyclohexane- or tetralin-fused (*Z*,*Z*)-1,4-bis(phosphino)-1,3-dienes **C**[13] and **D**[14] still show slow interconversion of the respective atropisomeric enantiomers in solution. Recently we disclosed that closely related (*Z*,*Z*)-1,4-bis(phosphinyl)-1,3-diene **E** could be resolved into the two *persistent* enantiomers, which did not racemize even at 135 °C.[14] Enantiomerically pure **E** thus obtained was applied as a Lewis base chiral organocatalyst in the asymmetric allylation of aldehydes with allylsilanes to show excellent enantioselectivity.[14] These observations have indicated the potential usefulness of the atropisomeric diene systems in asymmetric synthesis.

In this report, we would like to describe synthesis and characterization of novel C_2-symmetric *conformationally rigid* atropisomeric chiral diiododienes **1**.[15] Preformed racemic diiododienes **1a-c** were resolved by HPLC on a chiral stationary phase, and single-enantiomeric **1a-c** thus obtained were applied in the asymmetric dearomatizing spirolactonization as chiral organocatalysts to show good enantioselectivity in up to 73% ee.

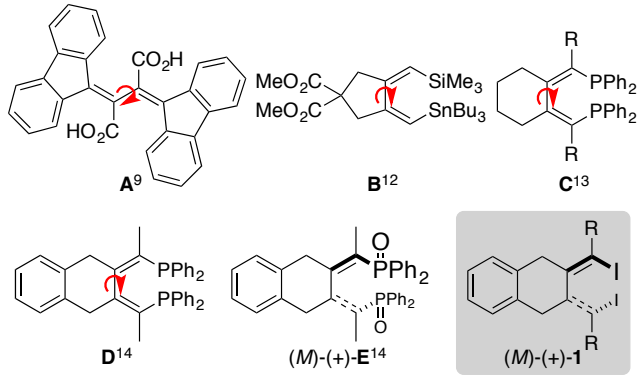
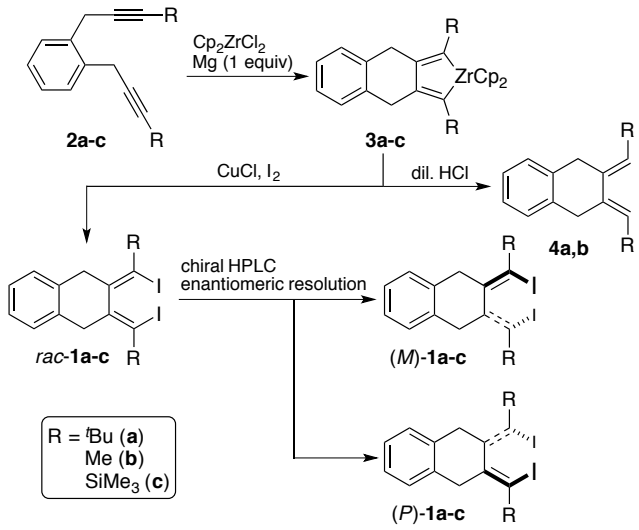


Figure 1. Atropisomerism in 1,3-dienes.

Treatment of 1,2-bis(4,4-dimethyl-2-pentynyl)benzene (**2a**) with Cp_2ZrCl_2/Mg[16] generated the corresponding zirconacyclopentadiene derivative **3a** in situ, and subsequently its iodolysis in the presence of CuCl followed by chromatographic purification gave **1a** in 40% yield as a colorless crystalline solid. Protonolysis of **3a** afforded homologous hydrocarbon **4a** in 45% yield as well (Scheme 1). In the same way, methyl-substituted **1b** and trimethylsilyl-substituted **1c**[17] were prepared in 68% and 41% yields, respectively.

Scheme 1. Synthesis and Enantiomeric Resolution of Atropisomeric Chiral Diiododienes 1



In the ^{1}H-NMR spectrum of **1a** recorded in $CDCl_3$, the methylene hydrogens at the 1- and 4-positions of the tetralin skeleton (H^a and H^b in Figure 2 (a)) were detected at δ 3.58 and 4.23 ($^2J_{HH}$ = 16.5 Hz) as a pair of well-resolved AB doublets. This observation implies that the two sterically demanding iodo-substituents in **1a** interact with each other, which prevents the molecule from taking the coplanar conformation. And thus, the diene-based atropisomeric axial chirality is induced in **1a**, and the two hydrogens in each CH_2 group are diastereotopic. The AB pattern in the ^{1}H-NMR spectrum was retained even at 140 °C in $CDCl_2CDCl_2$ and the signals showed no apparent broadening at this temperature. The NMR behavior indicated that **1a** showed no racemization or the racemization was much slower than the NMR time-scale. Methyl- or trimethylsilyl-substituted diiododienes, **1b** and **1c**, showed similar ^{1}H-NMR behavior as well. On the other hand, the two methylene hydrogens in closely related "hydro"-derivative **4a** are equivalent and detected as a sharp singlet in its ^{1}H-NMR spectrum (Figure 2 (b)) due to rapid rotation of the C2-C3 bond or planarity of the diene moiety (i.e., **4a** is achiral).

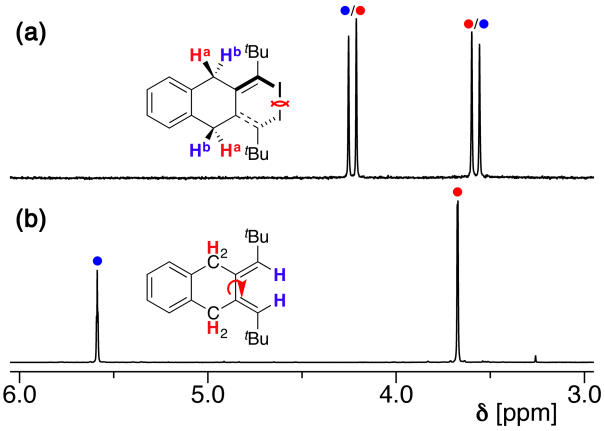


Figure 2. The ^{1}H-NMR spectra of (a) 1a and (b) 4a in the benzylic/olefinic region at 400 MHz in $CDCl_3$ at 23 °C.

The ^{1}H-NMR behavior of **1a** postulates that the compound is atropisomeric and the respective enantiomers may be separated as optically active species. Indeed, **1a** could be resolved into the two atropenantiomers in practically enantiomerically pure forms (>99.9% ee) by HPLC on a chiral stationary phase column (Daicel Chiralcel OD-H) using hexane as an eluent (Figure 3). Diiododiene **1a** displayed remarkable conformational rigidity with respect to the dienic axial chirality. The fast-eluting enantiomer of **1a** on an OD-H column is dextrorotatory ($[\alpha]_D^{21}$ = +63.6 (*c* 0.33, $CHCl_3$)). The resolved single-enantiomeric sample of (+)-**1a** was dissolved in mesitylene and heated at 150 °C for 12 h in the dark. After this time, the chiral HPLC analysis of (+)-**1a** showed no signs of racemization. On the basis of an assumed detection limit of 0.1% ee for this HPLC analysis, we estimated the lower limit of the activation energy of the atropisomeric racemization of **1a** at 150 °C to be $\Delta G^{\ddagger}$(423 K) ≥ 39.8 kcal/mol. This energy barrier in **1a** is high enough to prevent the compound from racemization, and indeed, the resolved sample of (–)-**1a** (>99.9% ee) kept at –30 °C for more than a year has retained its enantiomeric homogeneity.

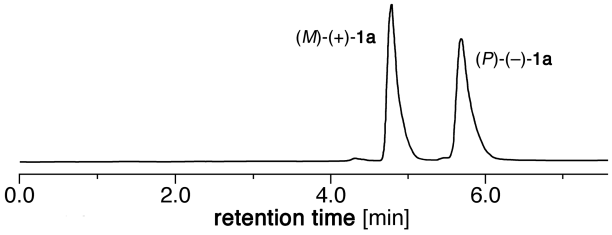


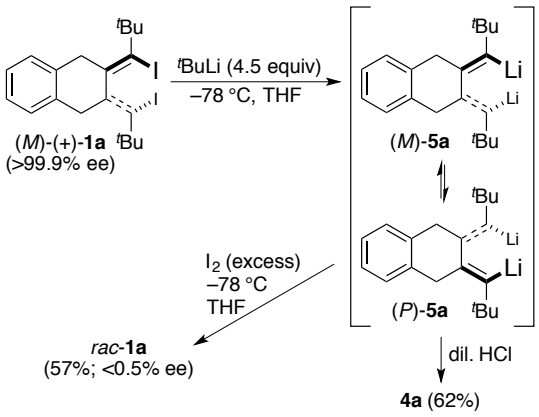
Figure 3. HPLC trace for *rac*-1a on a Daicel Chiralcel OD-H column (i.d., 4.6 mm; eluent, hexane; flow rate, 1.0 mL/min).

Both diiododienes **1b** and **1c** could be resolved into the respective "persistent" enantiomers by HPLC on a chiral stationary phase column as well (Daicel Chiralpak IB for **1b**; Chiralpak IA for **1c**. See Supporting Information for details).

The presence of the sterically demanding iodo-substituents in **1** is crucial for the conformational rigidity of the molecules. Treatment of (*M*)-(+)-**1a** (>99.9% ee) with ^{t}BuLi (4.5 equiv to **1a**) in THF at –78 °C generated dilithio-derivative **5a** in situ (confirmed by its protonolysis giving **4a**), and the subsequent reaction of **5a** with excess iodine at –78 °C re-generated **1a** in 57% yield. The

chiral HPLC analysis of recovered **1a** revealed that the compound was nearly racemic (<0.5% ee). Considering the conformational rigidity of **1a** (vide supra), the racemization could be attributed to the conformational fluxionality of **5a** which is with the much more compact lithio-substituents instead of the two iodo-substituents in **1a**. These observations are consistent with the reported behavior of binaphthyl derivatives; while axially chiral 2,2'-diiodo-1,1'-binaphthyl can be resolved into the respective "persistent" atropenantiomers, the corresponding 2,2'-dilithio-derivative racemizes easily.[18]

Scheme 2. Lithiation of (*M*)-(+)-1a and Iodolysis Forming *rac*-1a.



Dextrorotatory **1a** was recrystallized from cold pentane yielding colorless needles suitable for X-ray analysis. The Flack parameter was determined to be –0.05(3) for the structure shown in Figure 4, and the absolute configuration of (+)-**1a** is unambiguously assigned to be (*M*) (see Supporting Information for details). As shown in Figure 4, the array of the six atoms I(1)-C(1)-C(2)-C(11)-C(12)-I(2) constructs a characteristic helical motif in (+)-**1a**. The two iodine atoms, I(1) and I(2), considerably interact with each other, which should be a major factor preventing **1a** from racemization.

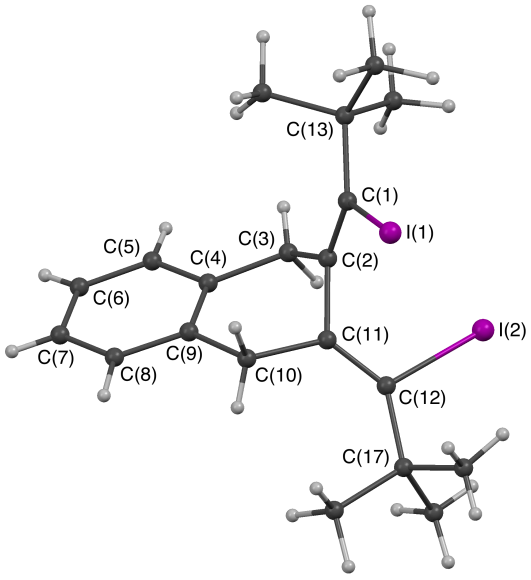
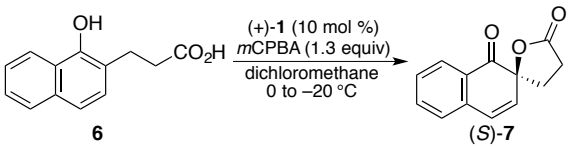


Figure 4. Ball-and-stick drawing of the single-crystal X-ray structure of (*M*)-(+)-1a with selected atom numbering.

We next investigated the potential of novel atropisomeric diiododienes (+)-**1a-c** as chiral organocatalysts in the asymmetric dearomatizing spirolactonization of 3-(1-hydroxy-2-naphthyl)propionic acid **6**,[19,20] and the results are summarized in Table 1. The reaction is mediated by a hypervalent iodine(III) species,[21,22] and the oxidative cyclization creates a chiral spirocarbon atom in lactone **7**.

Under the conditions shown in entry 1, i.e. in the presence of "wet" *m*-chloroperbenzoic acid (*m*CPBA containing 31% H_2O; 1.3 equiv to **6**) and (*M*)-(+)-**1a** (10 mol %) in dichloromethane at 0 °C, the oxidative cyclization of substrate **6** proceeded smoothly to give desired spirolactone **7** in 52% yield with 47% ee. Whereas the catalytically active hypervalent iodine(III) species[23] had low solubility in dichloromethane, conducting the reaction at lower concentration improved both chemical yield and enantioselectivity slightly (entry 2). While spirolactone **7** obtained using (+)-**1a** was levorotatory, that is with the (*S*)-stereogenic carbon atom, the reaction catalyzed by (+)-**1b** afforded dextrorotatory (*R*)-**7** in 45% ee and 47% yield (entry 3). Both **1a** and **1b** decomposed slowly at room temperature in the presence of wet *m*CPBA, and thus, they could not be recovered from the reaction mixture. On the other hand, Me_3Si-substituted counterpart **1c** showed better stability under the same conditions, and ca. 50% of **1c** was recovered from the catalytic reaction mixture. Due probably to the higher robustness, (+)-**1c** showed the better catalytic activity than **1a** and **1b** (entries 4-6). In addition, **1c** was found to be the most enantioselective among the three diiododienes. The reaction catalyzed by (+)-**1c** afforded (*S*)-**7** in 64% ee (entry 4). It was found that addition of acetic acid (6 equiv to **6**) was effective for preventing precipitation of the reactive hypervalent iodine(III) species, and (*S*)-**7** was obtained in 77% yield and in 69% ee (entry 5). Lowering the reaction temperature to –20 °C further improved the results giving (*S*)-**7** of 73% ee in 85% yield under the optimized conditions (entry 6). It should be mentioned that, to the best of our knowledge, diiododienes **1** are the first examples of "non-aryl" organic iodides serving for the λ^3-iodane-mediated asymmetric hypervalent iodine organocatalysis.[23]

Table 1. Asymmetric Dearomatizing Spirolactonization of 6 Catalyzed by C_2-Symmetric Atropisomeric Diiododienes 1[a]



6 (*S*)-**7**

entry	cat.	additive	temp	time	yield[b]	% ee[c]
1[d]	(+)-**1a**	none	0 °C	16 h	52%	47 (*S*)
2	(+)-**1a**	none	0 °C	20 h	57%	52 (*S*)
3	(+)-**1b**	none	0 °C	20 h	47%	45 (*R*)
4	(+)-**1c**	none	0 °C	20 h	60%	64 (*S*)
5	(+)-**1c**	AcOH[e]	0 °C	15 h	77%	69 (*S*)
6	(+)-**1c**	AcOH[e]	–20 °C	39 h	85%	73 (*S*)

[a] The reaction was conducted with 10 mol % of diiododiene **1** at 0.005 M concentration of substrate **6**. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel OD-H). The absolute configuration of **7** in parentheses. [d] 0.01 M concentration of substrate **6**. [e] 6 equiv to **6**.

In summary, we have found out that C_2-symmetric tetralin-fused 1,4-diiodo-1,3-butadiene derivatives, (*Z*,*Z*)-2,3-di(1-

iodoalkylidene)tetralin **1a-c**, are atropisomeric and conformationally persistent. After the enantiomeric resolution of the preformed racemates, the single-enantiomeric compounds were applied as chiral organocatalysts in the oxidative spirolactonization of **6** to show good performances with up to 73 % ee.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: *********. Experimental procedures, compound characterization data, and crystallographic data of (*M*)-(+)-**1a** (CIF file).

AUTHOR INFORMATION

Corresponding Author

ogasawar@tokushima-u.ac.jp (M. O.)
td1203@ph.ritsumei.ac.jp (T. D.)

ORCID

Masamichi Ogasawara: 0000-0002-1893-3306
Tamotsu Takahashi: 0000-0003-4728-6547
Toshifumi Dohi: 0000-0002-2812-9581

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid for Scientific Research (B) to M.O. (Grant #15H03805) from MEXT, Japan and a Grant-in-Aid for Scientific Research (C) to T.D. (Grant #16K08186) from MEXT, Japan. T.D. also thanks the Asahi Glass Foundation.

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